

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON AGING

Summary Minutes

The 138th Meeting

NATIONAL ADVISORY COUNCIL ON AGING

September 10–11, 2019

**National Institutes of Health
6001 Executive Blvd, Room C
Bethesda, MD 20892**

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Department of Health and Human Services
Public Health Service
National Institutes of Health
National Institute on Aging

**NATIONAL ADVISORY COUNCIL ON AGING
SUMMARY MINUTES
September 10-11, 2019**

The 138th meeting of the National Advisory Council on Aging (NACA) was convened on Tuesday, September 10, 2019, at 3 p.m. at 6001 Executive Blvd, Room C, National Institutes of Health (NIH), Bethesda, Maryland. Dr. Richard Hodes, Director, National Institute on Aging (NIA), presided.

In accordance with the provisions of Public Law 92–463, the meeting was closed to the public on Tuesday, September 10, from 3 p.m. to 5 p.m. for the review, discussion, and evaluation of grant applications in accordance with the provisions set forth in Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of Public Law 92–463.¹ The meeting was open to the public on Wednesday, September 11, from 8:00 a.m. to 1:15 p.m.

Council Participants:

Mr. James Appleby
Dr. David A. Bennett
Dr. Shalender Bhasin
Ms. Meryl Comer
Dr. Eileen M. Crimmins
Dr. Margaret A. Goodell
Dr. J Taylor Harden
Dr. David M. Holtzman
Dr. Stephen B. Kritchevsky
Dr. Terrie E. Moffitt
Ms. Susan K. Peschin
Dr. Eric Michael Reiman
Dr. Clifford James Rosen
Dr. Amy Jo Wagers
Dr. Keith E. Whitfield

Ad Hoc Participants:

Dr. Monica A. Driscoll

Ex Officio Participants:

Dr. Sarah Ruiz, Administration for Community Living

¹ For the record, it is noted that members absented themselves from the meeting when the Council discussed applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure only applied to applications that were discussed individually, not to “en bloc” actions.

The Council Roster, which gives titles, affiliations, and terms of appointment, is appended to these minutes as Attachment A.

In Addition to NIA Staff, Other Federal Employees Present:

Mrs. Valerie Cosby, National Institute of Diabetes and Digestive and Kidney Diseases, NIH
Dr. Michael S. Lauer, Deputy Director for Extramural Research, NIH

Members of the Public Present:

Dr. Kelly Beazley, Rose Li and Associates, Inc.
Dr. Sharon L. Christ, Purdue University
Ms. Trish D'Antonio, Gerontological Society of America
Dr. Andy DeSoto, Association for Psychological Science
Dr. Perry Kirkham, Purdue University
Dr. William E. Kraus, Duke University
Dr. Changhan David Lee, University of Southern California
Dr. Rose Maria Li, Rose Li and Associates, Inc.
Dr. Archana Singh-Manoux, The Institut National de la Santé et de la Recherche Médicale, France

I. REVIEW OF APPLICATIONS

This portion of the meeting was closed to the public, in accordance with the determination that it concerned matters exempt from mandatory disclosure under Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).²

A total of 1820 applications requesting \$ 4,298,768,312 for all years underwent initial review. The Council recommended 950 awards for a total of \$ 2,476,554,430 for all years. The actual funding of the awards recommended is determined by the availability of funds, percentile ranks, priority scores, and program relevance.

II. CALL TO ORDER

Dr. Hodes welcomed members to the open session of the 138th NACA meeting and called the meeting to order at 8:00 a.m. on Wednesday, September 11, 2019.

A. Director's Status Report

Dr. Hodes reported that the U.S. House bill includes an increase of \$2 billion for NIH and a 6.6% increase for NIA in its Fiscal Year 2020 budget, with no explicit mention of targeted funds. No action has been taken on this bill. The Senate has not yet released its version of an appropriations bill, but reports indicate it will likely include an increase of \$350 million for research on Alzheimer's disease (AD). Dr. Hodes speculated that the House and Senate are unlikely to agree

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on a budget before the end of FY 2019 and that the Government will likely operate under a continuing resolution.

Dr. Hodes also reported that the bypass budget for AD has been put forward for FY 2021. Accounting for targeted funds expected to become available in 2021, along with the assumption that the President's proposed budget will include a reduction in the NIH budget, the bypass budget for FY 2021 requests a total of \$2.8 billion in targeted funds. Dr. Hodes noted that the FY21 bypass budget includes input from the two most recent Summits—the 2017 Summit on Care and Services and the 2018 AD Summit—along with informal input from the 2019 Summit on AD and Related Dementias (ADRD), which had not yet formalized its recommendations at the time the bypass budget was developed. He also noted that 18 NIH Institutes and Centers (ICs) had participated in developing the bypass budget. Dr. Hodes reminded Council members that the bypass budgets not only estimate the amount of funding to reach research milestones in AD, but also provide a narrative that describes past accomplishments and future plans. Milestones are public, and a web-based tool is available for both NIH and the public to track funding.

Dr. Hodes then turned to NIA updates. He reported that NIA staff met with Representative Gus Bilirakis, of Florida, for an office briefing in June; Representative Maxine Waters, of California, at a Congressional Briefing hosted by Friends of the NIA; and the Congressional Task Force on Down Syndrome at a meet-and-greet. Other notable events include a meeting between Dr. Hodes and Washington Senator Patty Murray; a meeting between NIA staff and staff in the Office of Representative Earl Blumenauer; a briefing on AD clinical trials to the Senate Appropriations Committee and clerks for the Education Majority and Minority Leaders; and a briefing for the Senate Aging Committee, by NIA and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development staff, on research in AD and Down Syndrome.

Dr. Hodes noted that September is Go4Life month, a longstanding, evidence-based promotion of physical activity. He also noted the upcoming Director's Regional Meeting, which will be held November 7, 2019, at the University of Southern Maine. The Third Geroscience Summit will be held November 4–5, 2019, at Natcher Conference Center, the Second Dementia Care Summit will be held March 24–25, 2020, and the Second NIH Workshop on Inclusion Across the Lifespan will be held on September 2–3, 2020.

Dr. Hodes closed his presentation by noting resolutions by Dr. Francis Collins, NIH Director, and many IC leaders regarding diversity in meeting participation at all levels. Dr. Collins announced that his attendance at conferences would depend on the balance in gender composition among speakers and leadership. Dr. Hodes intends to follow this example.

Dr. Hodes also recognized Dr. John Haaga, Director of the Division of Behavioral and Social Research (DBSR), who will be retiring at the end of this year.

Ms. Susan Peschin expressed excitement about NIH efforts toward inclusion across the lifespan. She recommended that the second inclusion workshop include the European Medicines Agency, which has developed a Geriatrics Medicines Strategy that requires even industry-sponsored trials to include individuals across the lifespan and with multiple chronic conditions. She cited Francesca Cerreta as a potential contact.

B. Future Meeting Dates

January 21–22, 2020 (Tuesday and Wednesday, TBD)

May 26–27, 2020 (Tuesday and Wednesday, TBD)

September 8–9, 2020 (Tuesday and Wednesday, Building 45)

C. Consideration of Minutes of the Last Meeting

The minutes of the May 2019 meeting were considered. A motion to approve the minutes was made, seconded, and passed unanimously.

III. REPORT: TASK FORCE ON MINORITY AGING RESEARCH

Dr. J Taylor Harden, Task Force Co-Chair, began her presentation by reminding Council of presentations from the May meeting on inclusion of sex and gender minorities in research and on AD RD among Native populations. She reported that, on the previous day, the Task Force had heard presentations from Drs. Robin Barr and Charlene LeFauve and information updates from Drs. Mia Lowden and Jaron Lockett.

Dr. Barr's presentation focused on the Working Group for the triennial NIA Inclusion Report. This Working Group has been established to aid NIA in improving the Report by adding or incorporating data on retention and on the minimum and maximum ages of study participants. NIA is also expected to automate targeted enrollment data soon. The Task Force plans to invite the NIH Inclusion Policy Officer to give an update at the January 2020 Council meeting.

The presentation by Dr. LeFauve, Senior Advisor to the Chief Officer for Scientific Workforce Diversity, reported on NIH's efforts to address concerns raised in 2011 by the Ginther report, which had reported racial and ethnic disparities in research awards from NIH. The NIH Office of Scientific Workforce Diversity has focused its efforts on four key areas—mentoring, pipeline, infrastructure, and peer review—and these efforts have led to increased success rates among applicants from underrepresented minority groups. However, problems remain with attrition, particularly in the transition from K awards to R01s, and the number of researchers from underrepresented minority groups that remain in faculty positions remains low, perpetuating the gap in R01 funding. In response to recommendations made by a working group of the Advisory Council to the Director in 2017, the Office has developed a template for reporting on diversity and inclusion metrics, focused on institutional approaches to facilitate the transition to career independence, and held a national conference on programs advancing diversity. It also is developing trans-agency standards to ensure comparability and consistency in the Diversity Supplements program.

Dr. Harden concluded her report with informational updates provided by Drs. Lowden and Lockett. She noted again the upcoming NIA Director's Regional Meeting on Aging Research. She also noted that, as a result of efforts by the Women of Color Committee and the trans-NIH Special Populations Group, four women of color will be speaking as part of the NIH Director's Wednesday Afternoon Lectures series. Dr. Harden reported that the 2019 Butler-Williams Scholars Program was another success, with 50 scholars selected from 241 applications representing 22 states and 100 scientific disciplines. The 2020 program will be held July 6–10, 2020, and the application period will open in October 2019. Dr. Harden expressed the Task

Force's hope that the program could be expanded to twice a year and/or accommodate more participants.

Dr. David Bennett, Task Force Co-Chair, noted a conversation with Dr. Lockett, who had reported that, of applicants who did not receive invitations to the Butler-Williams Scholars program, 15 to 25 represented "gut-wrenching" decisions for NIA. Dr. Bennett acknowledged the time commitment of the program and issues with space but suggested that NIA consider how to accommodate these 15 to 25 applicants. In response to questions from other Council members about interactions with parallel initiatives, Dr. Harden noted NIH's and NIA's long history of working synergistically with these organizations and programs.

In response to questions from Dr. Sarah Ruiz, Dr. Harden acknowledged that the Task Force has not specifically mentioned persons with disabilities and suggested this group as a topic for further discussion by the Task Force and Council. Dr. Marie Bernard, NIA Deputy Director, added that NIA participates in the National Academies Forum on Aging, Disability, and Independence and suggested that updates from this Forum could be presented to the Task Force. Dr. Barr also noted that NIA's diversity programs include disability as a category.

IV. REPORT: WORKING GROUP ON PROGRAM

A. RFA/RFP Concept Clearances

Dr. Eileen Crimmins reported that the Working Group reviewed 15 concept clearance requests and recommended them for approval. The Council made and seconded a motion to approve these concepts en bloc. The motion passed unanimously.

Mechanisms of Rejuvenation and Accelerated Aging in Heterochronic Blood Exchange Experiments

The proposed concept will support research dissecting mechanisms underlying the change in phenotypes resulting from heterochronic blood exchange. The Working Group noted that this presents a unique approach to understanding aging biology and could identify manipulatable mechanisms to slow or reverse age-related deterioration through experiments that could be done fairly rapidly. The Working Group suggested that the concept be open to a broad array of experimental approaches and not just to surgical fusion and parabiosis.

New/Unconventional Animal Models of AD

The proposed concept will support research to develop models in animals other than mice, to complement ongoing efforts in mouse models. The Working Group noted the need for such models both to improve understanding of AD-related pathology and various aspects of cognitive decline. The Working Group recommended that the concept be broad enough, with respect to animals, for investigators to propose the best ideas.

Stem Cell Aging and Oncogenic Transformation

Deep sequencing of normal human tissue has shown an accumulation of somatic mutations, including many driver mutations associated with cancer. However, younger adults do not always

develop cancer, suggesting that aging-related changes in the environment promote oncogenic transformation. The proposed concept, a collaboration between NIA and the National Cancer Institute, will support research to understand these changes in the environment. The Working Group expressed enthusiasm for this proposal and noted the timeliness of the concept.

Emotional Wellbeing Networks

Wellbeing is a complex, multifaceted concept that involves more than merely the absence of disease. The proposed concept, developed by the National Center for Complementary and Integrative Health and the NIH Office of Behavioral and Social Sciences Research, aims to establish networks to explore the role of wellbeing in health, identify measures, and work toward new interventions to promote wellbeing. NIA will be one of the ICs participating in the concept. The Working Group suggested that the concept incorporate wording about cultural factors that influence the connection between wellbeing and health, because there may be health disparities in wellbeing as in other aspects of health. However, the Working Group was enthusiastic about the proposal and noted its relevance to many of NIA's strategic goals.

National Longitudinal Study of Adolescent to Adult Health (Ad-Health), Wave 6

This concept represents efforts by DBSR to incorporate cohort studies that have already collected prospective data. This longitudinal study, also known as Ad-Health, has several advantages. Recruiting new cohorts at midlife is proving increasingly difficult, and this concept would extend cohorts that have already been studied, have good will toward participating in research, and could feed into refresher panels for the Health and Retirement Study (HRS). Ad-Health was also designed originally to collect data on the contexts of family, peer and social networks, and neighborhoods. The study has already collected costly measures such as DNA and RNA, and many data users from the field of child and adolescent development would likely follow the data and develop research programs related to aging, thereby injecting a fresh cadre of behavioral and social scientists. The Working Group recommended that NIA clarify details about attrition, attrition bias, and representation of African- and Asian-American groups. The Working Group also recommended that NIA ensure that measures between Ad-Health and HRS be harmonized.

Technology Resource Centers for Aging Research

This concept will support centers to develop strategies, tools, methods, and recommendations to leverage technology and enable individuals to live healthy and independent lives. The concept will support and scale up new and existing efforts. Each center is expected to include seven cores, one of which would be proposed by the principal investigator, and the program will include a coordinating center. The Working Group suggested that some core functions be centralized at the coordinating center, each center include an older adult patient, family member, or caregiver as an advisor on projects, and "coverage" be added to the purview of the core focused on reimbursement.

Aging Research Dissertation Awards to Increase Diversity

The proposed concept will add to ongoing efforts to increase workforce diversity by increasing the number of trained researchers from underrepresented groups; improving recruitment of

talented researchers; improving the quality of the training environment and educational opportunities; and improving capacity to address and eliminate health disparities. The Working Group noted satisfactory responses from NIA with respect to the number of positions and applicants funded and data on the impact of the program.

Planning Projects for Clinical Trials on Reductions in Caloric Intake and Related Dietary Practices

Caloric restriction has proven to be efficacious in extending health- and lifespan across animal species, and the 2-year Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) study has shown that moderate reductions in energy intake is feasible and improves cardiometabolic risk factors and inflammatory markers. The proposed concept will support two or more planning projects to develop long-term studies on interventions that mimic caloric restriction to determine whether these interventions are clinically effective. The Working Group agreed on the need for a funding opportunity to incentivize strong grant proposals and noted that this is one of the most important initiatives in aging research.

Research Education Resources to Foster Development of Geriatrics-Related Translational and Clinical Scientists

The proposed concept will provide educational resources for developing a new generation of geriatric clinician-scientists. The focus of these resources will include clinical investigation skills, clinical trials of geroscience-related interventions, and functional outcomes for clinical trials and disease management. The awards will support the development and wider dissemination of these resources in areas such as curricula, skills training, research experiences, and criteria for competency. The target audience would span from undergraduates to new faculty and include nurses, dentists, pharmacists, social workers, and those from diverse backgrounds. NIA staff answered questions about priorities and how this program would be conducted.

AD Sequencing Project (ADSP) Functional Genomics Program (FGP)

Several NIA-supported efforts have identified genomic variants associated with ADRD. Many of these variants appear in noncoding regions of the genome, but the functional effects of these variations are not clear. The proposed concept will support mapping of the genome and epigenome and the annotation of these elements. It will coordinate efforts to functionally validate and prioritize discoveries. The Working Group noted that this represents a high priority for NIA with respect to ADRD genetics.

Central and Peripheral Control of Balance in Older Adults

Balance disorders are prevalent among older adults and increase their risk for falls, injuries, mobility problems, and loss of independence. Maintaining balance during static and dynamic conditions requires the complex integration of many physiologic systems, and systematic investigations of these mechanisms are needed. Informed by a workshop held on this topic earlier in 2019, the proposed concept will support studies on central and peripheral control of balance in older adults and animal models. The Working Group agreed that this is an important area of research.

Glial Plasticity in the Aging Brain

Glia outnumber neurons four to one and play an important role in normal brain function and many diseases. However, the heterogeneity and role of various glial subtypes, and how they change in the aging brain, are poorly understood. The proposed concept will support research on the heterogeneity and function of glia during aging. The Working Group suggested that the concept include the study of diseased brains to compare disease-related changes to those associated with normal aging.

Harmonization of AD and ADRD Genetic, Epidemiologic, and Clinical Data

With ongoing, large-scale genetic discovery, especially of rare variants, there is a need to pull information from several datasets. Each dataset, while rich with genotypic and phenotypic data, is collected differently. This concept will support a U24 cooperative agreement to harmonize approaches across these cohorts. The Working Group supported the concept as written.

Oligomer Seed Bank Initiative

The accumulation of protease-resistant aggregates is poorly understood. There is a wide variety of oligomers with different names, and it is not clear whether the names reflect different oligomers or refer to the same oligomers. The proposed concept will support one to three centralized centers to catalog these oligomers. The Working Group noted that this concept represented a high priority for NIA and was highly supportive of it.

Prodromal Alpha-Synucleinopathies Consortium

Parasomnia, in which motor function is not suppressed during REM sleep, can occur in the presence of neurological disease or be a precursor to alpha-synucleinopathies such as Parkinson's disease. The proposed concept will support systematic research to study cognition and biomarkers associated with parasomnia and to develop a trial-ready cohort. The Working Group supported the concept as written.

B. Review of the Division of Behavioral and Social Research (DBSR)

Dr. Terrie Moffitt reported that the review panel met on Monday, September 9, to review a draft report resulting from work done during an in-person meeting in May and a series of conference calls over the summer. She noted that overall the DBSR review appears to be on track. The report, which will include recommendations for the next 10 years, should be finalized by the end of the year and will be presented at the January Council meeting.

V. COMMENTS FROM RETIRING COUNCIL MEMBERS

Dr. Hodes recognized two outgoing members: Dr. Crimmins and Dr. Moffitt.

Dr. Crimmins noted that she had enjoyed her experience on the Council and acknowledged her fellow members as busy people who do their jobs well and are scientifically directed, open-minded, and committed. She also acknowledged the selflessness and dedication of the NIA staff and increased camaraderie and integration she has seen across all NIA Divisions.

Dr. Moffitt reminded the Council that she is a relatively new researcher in the field of aging, having spent most of her career in studying child development. She thanked NIA and her fellow Council members for giving her a warm welcome and likened her time in the Working Group on Program and the Task Force on Minority Aging Research to a postdoctoral fellowship in aging research because of how much she learned. She also expressed excitement to have served on the Council during a time of unprecedented expansion in AD-targeted funding. Dr. Moffitt also acknowledged the dedication of the NIA staff, which has worked under enormous pressure in response to this expansion. She acknowledged Dr. Barr's role as Executive Secretary and thanked Ms. Diane Zwinak for her help with Council management.

VI. GUEST SPEAKER: FOREIGN GOVERNMENT'S RESEARCH EFFORTS AND THE EFFECTS ON U.S.-BASED INVESTIGATORS

Dr. Michael Lauer, Deputy Director for Extramural Research, NIH, addressed the issue of China's Thousand Talents Program, which aims to lure Chinese-born scientists and recruit highly skilled foreign researchers to China, is now in its tenth year. To obtain an award as part of this program, scientists must demonstrate employment at or have a job offer with a Chinese institution. According to one report from the Hoover Institution at Stanford University, more than 300 U.S. government researchers and corporate personnel have received funds from and employment through the Thousand Talents Program and similar programs in China, but in many cases, they have not disclosed these awards. Employment contracts with Chinese institutions, many of which outline full-time commitments despite those scientists being employed at U.S. institutions, specify clear deliverables including publications, intellectual property, and training affiliated primarily with the Chinese institutions. The contracts might establish a shadow laboratory, whereby all the work is done in a U.S. laboratory, and the Chinese laboratory receives important information and intellectual property. They may also produce duplicate grants, in which the specific aims in Chinese grants are identical to those in grants funded by the U.S. NIH. In many cases, the appearance of Chinese institutions and Chinese grants in the acknowledgment sections of publications provides the only indication of these other commitments. In addition to issues with commitments and duplicate employment and grants, there also have been cases of undisclosed business interests and peer review breaches.

Dr. Lauer described efforts to address these concerns. So far, NIH has identified more than 100 scientists of concern and has reached out to more than 65 institutions that have been affected. NIH has suspended funds for relevant researchers, received refunds of overcharges, renegotiated grant terms and conditions, and, in the case of duplications, terminated grants altogether. NIH is also working with the Office of Inspector General, the Federal Bureau of Investigations, the State Department, and other Federal agencies to seek debarment or suspension of investigators in certain cases. U.S. institutions are becoming increasingly aware of the concerns. Dr. Lauer emphasized that collaboration with Chinese and other international institutions is acceptable. However, legitimate international collaborations must be disclosed and vetted to identify potential conflicts of interest, duplications of research, and potential for diversion of intellectual property.

In response to questions about how to address these problems early in the hiring process, Dr. Lauer noted that NIH has been working with provosts and that the Association of American Universities and the Association of Public and Land-Grant Universities have published

documents outlining best practices. He also noted that, so far, NIH has focused primarily on principal investigators. However, a youth Talents program primarily targets early-stage investigators, and NIH has learned of cases where postdoctoral fellows were supported by China and NIH at the same time; in those cases, NIH received refunds. Although 95% of cases involve China, it is not the only country providing undisclosed support. Dr. Lauer reiterated that legitimate collaborations are transparent, that leadership from all institutions are aware of the collaboration, and that the agreement specifies roles and responsibilities, what materials are shared, and who owns what intellectual property.

VII. PROGRAM HIGHLIGHTS

A. Division of Neuroscience: Religious Orders Study and Rush Memory and Aging Project: Roadmap to ADRD Precision Medicine

Dr. David Bennett, Director, Rush Alzheimer's Disease Center introduced the Religious Orders Study. The study began in 1993, and has enrolled approximately 15,000 nuns, priests, and brothers without known dementia from across the United States. At the time of enrollment, all participants agreed to clinical evaluations and, upon their deaths, brain donations. Since then, 600 participants have developed mild cognitive impairment (MCI) and 375 have developed dementia, and the study has performed 775 brain autopsies. The Rush Memory and Aging Project, which began in 1997, has enrolled 2,200 residents from the Chicago metropolitan area. As with the Religious Orders Study, all participants agreed to clinical evaluations and, at the time of their deaths, donations of brain, spinal cord, muscle, and nerves. More than 625 of these participants have developed MCI and 375 have developed dementia, and the project has performed 850 autopsies. Both studies follow participants prospectively; have captured genomic/proteomic, experiential, psychological, behavioral, medical, and economic factors; and have measured several AD pathologies. The studies have also identified resilience factors. Both studies were designed to follow participants prospectively, capture a variety of phenotypes, and collect information on biology and risk factors underlying disease and changes in function. The same team, manager, coordinator, testers, and nurses are running both studies, and data from these studies can be merged for analysis.

Dr. Bennett noted that all of the pathologies captured by the Religious Orders Study and the Rush Memory and Aging Project explain approximately two-thirds of AD dementia cases. Although more than 250 combined pathologies have been measured across 1,000 participants, no one combination is present in greater than 6% of participants. Depending on what else is happening in a participant's brain, the contribution of each AD-related pathology to an individual's cognitive decline ranges from 20% to 100%. In a phenome-wide association study, plasticity protein NRN1 has been identified as a potential contributor to cognitive decline independent of other pathologies.

Over the past decade, the two studies have taken advantage of clinical and pathologic data, imaging, and various -omics and have followed a systems biology approach to develop a framework that might predict which factors are associated with cognitive decline and ADRD phenotypes. The studies will then conduct targeted proteomic studies from brain sections and ex vivo experiments to determine whether these are druggable targets. One approach involves the generation of induced pluripotent stem cells from the skin of autopsied participants, differentiate

them into neurons and astrocytes, then manipulate them in cellular and molecular assays, for example with CRISPR and tool compounds. By so doing, the study team is generating a roadmap of genomic and proteomic fingerprints that could predict therapeutic response, as well as potential compounds that could be developed or repurposed into new therapies.

Council discussion focused on technical aspects of this work.

B. Division of Geriatrics and Clinical Gerontology: CALERIE: Two Years of Calorie Restriction in Humans: Effects on Lifespan and Healthspan

Dr. William Krause, of Duke University, highlighted data from the CALERIE study. As was discussed earlier at this meeting, studies across animal models have demonstrated that caloric restriction increases both healthspan and lifespan. Likewise, a study in Biosphere 2 and a long-term study conducted on a group of individuals who had self-imposed caloric restriction suggested that caloric restriction might also be beneficial to humans with respect to cardiometabolic factors. On the basis of these findings, the CALERIE study has assessed potential time-course effects of calorie restriction on cardiometabolic risk factors and markers of aging, potential differences between the weight-loss and weight-maintenance phases, and the safety of such an approach.

In a paper published this summer in *Lancet Diabetes and Endocrinology*, the CALERIE study reported that 2 years of moderate caloric restriction, in a high body mass index and in a lower body mass index group, significantly reduces cardiometabolic risk factors (blood pressure, cholesterol, glucose control, and insulin sensitivity) in non-obese young adults, providing a substantial advantage for future cardiovascular health. Most of these factors showed a response during the 12-month weight-loss phase but improved even more substantially during the subsequent 12-month weight-maintenance phase. Group differences (ad libitum compared to restricted diet) were more pronounced among the high body mass index group than the low body mass index group. But this pattern arose because of differences in how the two ad libitum groups behaved. The high body mass control group gained body mass during the trial. The lower body mass group lost body mass. This control group appeared to engage in some spontaneous dieting on their own. Another CALERIE-based study has shown sex differences in changes in body composition, despite comparable differences in total body mass. Yet other studies have shown that caloric restriction improves mood, quality of life, sleep, and sexual function; may affect reactive oxygen species; and modifies biological aging. Studies are under way to identify the cellular and molecular mechanisms underlying these effects.

Council discussion focused on technical aspects of the CALERIE study and alternative approaches such as alternate day fasting.

C. Division of Aging Biology: Longevity Genes and the Mitochondrial Genome

Dr. Changyan David Lee, of the University of Southern California, discussed the Endosymbiotic Theory, which says that our ancestral cells joined with energy-efficient bacteria about 2 billion years ago. As a result, our ancestral cells became complex eukaryotic cells, in which the bacteria became an organelle, the mitochondria. This transition may have been mediated by a special

communication involving factors such as mitochondria-derived peptides. Dr. Lee shared his work on one such peptide, Mitochondria ORF from the Twelve-S rRNA type C (MOTS-C).

MOTS-C regulates cellular metabolism and improves insulin resistance, and in mouse studies it prevents weight gain even on a high-fat diet. Dr. Lee and his colleagues also have shown that MOTS-C expression increases with exercise, injection of MOTS-C improves running capacity among aged mice, and intermittent MOTS-C expression in late life increases lifespan. They also have found that MOTS-C expression increases in immune cells in response to interferon stimulation, consistent with its putative function as a bacterial immunity peptide. Likewise, the addition of MOTS-C to bacterial cultures induces agglutination similar to that observed with antibiotic treatment, and the literature suggests that bacterial immunity peptides have a primary role in immune modulation. In addition, MOTS-C normally resides outside the nucleus, but in times of cellular stress, it is translocated to the nucleus, where it regulates nuclear gene expression, inconsistent with our traditional understanding that the mitochondrial genome encodes structural genome while the nuclear genome encodes all the factors necessary to regulate cellular activity. On the basis of these findings, both genomes may encode factors important to our immune system, which could have implications for aging, inflammation, and immunity.

Council discussion focused on speculation about the implications of this work.

D. Division of Behavioral and Social Research: Life-Course Approach to Cognitive Aging and Dementia

Dr. Archana Singh-Manoux, of the Institut National de la Santé et de la Recherche Médicale in France, discussed a life-course approach to cognitive aging and dementia based on data from the Whitehall Study. She began by reminding Council members that evidence from the Whitehall Study and others show a gradual decline in cognitive function between the ages of 45 and 80 years and that this decline is heterogeneous. Yet the initial work in dementia research focused on individuals who were 65 years and older at baseline. Participants are at different points along their path to dementia at age 65. Any results will be a mix of participants earlier and later in their decline. Therefore, the age-based cut-off biases toward negative results through increased sample variability. Dr. Singh-Manoux and her colleagues anchor their analysis to the year when participants are diagnosed with dementia and then look at risk factors at specific time points before diagnosis. Dr. Singh-Manoux introduced the concept of reverse causality with an example involving late-life depression. Within the Whitehall study, individuals who subsequently develop dementia and individuals who do not show similar, low rates of depression earlier in life. However, individuals who develop dementia show increasing rates of depression as the time of diagnosis approaches. The parsimonious explanation is that an incipient cognitive decline provoked the depression rather than vice versa. She illustrated a similar pattern in the observed relationship of obesity to dementia. Earlier in life, increased weight is a modest risk factor for dementia. However, closer to the time of diagnosis individuals who become demented show accelerated weight loss.

Dr. Singh-Manoux then used the 10 years prior to diagnosis as a wash-out period to control for reverse causality effects. Instead, her team looked for relationships over the longer term. With that approach, Dr. Singh Manoux reported that neither physical activity, nor blood pressure, nor

quality of diet moderated risk for dementia. In contrast, atrial fibrillation, diagnosed hypertension, and American Heart Association cardiovascular health scores exacerbated risk of dementia among participants who showed no evidence of stroke.

Council discussion focused on technical aspects of Dr. Singh-Manoux's work and implications of her work for issues of reverse causation.

VIII. ADJOURNMENT

The open session of the 138th meeting of the National Advisory Council on Aging adjourned at 1:00 p.m. on September 11, 2019. The next meeting is scheduled for January 21–22, 2020.

IX. CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.³

Richard J. Hodes, M.D.
Chairman, National Advisory Council on Aging
Director, National Institute on Aging

Prepared by Robin Barr, D. Phil
With assistance by Rose Li and Associates, Inc.

³ These minutes will be approved formally by Council at the next meeting on January 21-22, 2020, and corrections or notations will be stated in the minutes of that meeting.